THE INDIVIDUALITY-DIFFERENTIAL AND ITS MODE OF INHERITANCE

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In a preceding communication we have shown that all the tissues of an individual have in common a chemical characteristic through which they differ from other individuals of the same species. This characteristic may be designated as the individuality-differential. It is probable that in the circulating body fluids these individuality-differentials or substances specifically adapted to them are likewise present. The interaction of cells and substances which possess the same individuality differential leads to the production of autosubstances which are responsible for various conditions of tissues. But if, through transplantation, the individuality-differentials become converted into syngenesio-, homoio- or heterodifferentials toxic substances are produced, the syngenesio-, homoio- or heterotoxins which lead to tissue reactions of different kinds as we have described in the preceding communication.

In the process of fertilization usually two homoio-differentials combine to form a new individual. Through transplantation of tissue it is possible to determine whether the individuality-differential of the child is identical with the individuality-differential of one of the two parents or whether its character is intermediate. If the inheritance of the individuality-differential should behave like a simple Mendelian monohybrid character, all the offspring of the first generation would have the same individuality-differential and the individuality-differential of one of the two parents would probably dominate.

Interchange of tissues between the children (brothers and sisters) should give results identical with those of autotransplantation, and transplantation of tissues from one of the two parents to a child should in all children give the same result, and the results should be those of either auto- or homoiotransplantation. Or, it might be possible that in the offspring a blending of the individuality-differentials of both parents occurs. It might furthermore be possible that in all children the same kind of blending occurred or that all intermediate degrees of blending of the differentials of father and mother be found.

In using transplantation of tissue as a means of determining which of these possibilities is realized, we have to take into account the difference in the situation of host and graft. Under the usual conditions of transplantation the host is a selfsufficient organism and is not in any essential manner dependent for his nourishment upon the graft. The graft on the contrary depends upon the host for its nourishment. The relation between host and graft is therefore not that of simple reciprocity. This relation may be important in interpreting certain results of transplantation as we shall see later.

We have carried out two series of experiments in which we analyzed the mode of inheritance of the individuality-differential, one in the rat[1] and a second one in the guinea pig.[2] In the former we transplanted simultaneously pieces from different organs into rats; in the second we used the thyroid gland for transplantation. We transplanted tissues from parents to children, from children to mother and from brothers to brothers. Both series, in the rat and guinea pig, gave the same result as far as the main problem is concerned; the individuality-differentials of the children are intermediate between those of the two parents; but all kinds of intermediate conditions

[1] Leo Loeb, *Journ. Med. Research*, 1918, XXXVIII, 393 (here the literature is discussed).

[2] Leo Loeb, *Journ. Med. Research*, 1918, XXXIX, 39.

are found varying between those approaching identity of individuality-differentials on the one extreme and homoio-differentials on the other.

In the guinea pig we analyzed further the difference in the results after transplantation of tissues from brother to brother, from mother to child and from child to mother. We found transplantation from brother to brother to give the best results, but even here the mixing of the individuality-differentials called forth the development of toxins, syngenesiotoxins, which usually were relatively mild, but in certain cases would be more severe. Transplantation from child to mother led to the production of toxic effects which were almost as marked as those produced by the homoio-toxins. Transplantation of tissues from mother to child on the whole resembled that of transplantation from brother to brother, but seemed to be somewhat less favorable. In the rat there were likewise indications that the transplantation from child to mother was more unfavorable than the others, but a decided difference between transplantations from mother to children and from brother to brother could so far not be established. However, the indicator of effects which we used in our guinea pig series was finer than that in our rat series.

We have begun experiments to determine the behavior of individuality-differentials in the second generation. It seems that here too the results are intermediate, but further experiments need to be carried out, before a definite statement can be made.

In a provisional way we may attempt to explain these results as follows. In most cases each individual has at least two sets of individuality-differentials, one inherited from the father, the other from the mother. Each set again consists of two kinds of differentials. There may be added individuality-differentials from some further distant ancestors, but this complication may be ignored at present; in certain individuals the differentials of either father or mother are lacking. We may assume

that several or all of the chromosomes of the father are characterized by certain chemical groups which would be the same in the cells of the same individual, but would differ in the cells of different individuals. Each cell of the child obtains a combination of chromosomes which is the same in the same individual, but differs in the case of different brothers or sisters. The chemical individuality-character of the chromosomes should lead to analogous chemical differences consisting perhaps in the formation of chemical sidechains attached to proteins; they should be present primarily in cell proteins and secondarily in the proteins of the body fluids. While the individuality-differentials in the tissues exist perhaps even in the embryo, there are some indications that the adapted substances in the body fluids originate after birth. These side chains must be identical in all the proteins of the same individual and differ in the case of different individuals. We should then expect that the individuality-differentials of the children, being a mixture of those of the parents, however in proportions which differ in the case of different children, should be intermediate between those of the parents. Extremes in the children may be almost identical with one or the other parent. In transplanting tissue from one brother to another the graft would in most cases find in the host the same characteristic groups which its own cells possess, but in a somewhat different quantitative relationship. Therefore the life of the graft which finds all the characteristic substances could be sustained; but the quantitative differences which exist in most cases would gradually lead to toxic effects which ultimately endanger the life of the graft. In some cases, however, the host would lack altogether some of the chromosomes or groups present in the brother and then the result would be more unfavorable, somewhat approaching that of homoiotransplantation.

In the case of transplantation from child to mother on the other hand the graft would lack one half the chromo-

somes and therefore the corresponding chemical groups present in the cells of the graft. The result should therefore approach that of homoio-transplantation, which we indeed find to be the case. After transplantation from mother to child the graft finds in the host in many cases the chemical groups it possesses itself, but again the proportion of chemical groups in host and graft (corresponding to that of the chromosomes) differs here more than in the case of two brothers and these quantitative differences might lead to a greater incompatibility between graft and host than in the case of transplantation from brother to brother. On this assumption we might furthermore expect that in certain rare cases even homoio-differentials should show a similar constitution and might therefore permit a successful transplantation into a not related individual.

While the somatic tissues require for their normal life identity of individuality differentials with which they come into contact, the germ cells on the contrary are normally adapted to contact with homoio-differentials in the chromosomes and as T. H. Morgan[3] has shown in Ciona secondary mechanisms may even make auto fertilization impossible.

In man, Landsteiner, Moss and others found a peculiar distribution of isoagglutinins into three or four groups, which are apparently independent of the parentage of the individuals concerned. Such a condition seems to be peculiar to man and has not been found in animals (Hecktoen).[4] In certain animals, however, von Dungern[5] and Hirschfeld succeeded through immunization to demonstrate the existence of two kinds of isohemagglutinins and of the corresponding antigens and thus of four classes of individuals. As our transplantations show conditions in the tissues cannot be the same as in the red blood corpuscles, if we should judge the constitution of

[3] T. H. Morgan, *Biological Bulletin*, 1905, VIII, 313.

[4] L. Hecktoen, *J. Infect. Diseases*, 1907, IV, 297.

[5] V. Dungern, *Munch. Med. Wok.*, 1910, Vol. 57, p. 293, p. 740.

the latter on the basis of these agglutination tests. In the case of the tissues we have to assume the existence of individuality-differentials which are composed of multiple chemical groups; therefore Mendelian heredity would be that of multiple factors. It is not improbable that even in the case of tissues the number of these groups is limited and that all the individuals of the same species have a choice only between a relatively small number of groups which is characteristic of each species and that the different individuals of a species differ from each other through the combination of these groups which each individual possesses. Other chemical groups would be characteristic of species and in this case also the number of groups which constitute a species differential may be limited.

The explanation for the facts of inheritance of the individuality-differentials which we attempted in this note is regarded by us at present as of an entirely provisional character. So far, however, it seems to agree with the facts as they are known; but we have no doubt that as investigations progress still further it may require certain, perhaps fargoing, modifications. It finds, however, support in the investigations of Landsteiner,[6] Pick and Obermeyer and others who have shown that the immune reaction-specificity of protein substances can be experimentally altered through changes in chemical side chains which are added to these proteins.

[6] Karl Landsteiner u. Hans Lampl, *Biochem. Zeitsch.*, 1918, LXXXVI, 342.